Remarks

Oath/Declaration

The Examiner has indicated that the Declaration is defective on the grounds that (i) it does not identify the mailing address of each inventor and (ii) it does not identify the U.S. provisional application to which priority is claimed. Applicants submit that the information missing in the Declaration is not necessary for further consideration of the claims and therefore, in accordance with 37 C.F.R. 111(b), Applicants hereby requests that the requirement to correct the defects be held in abeyance until an indication of allowable subject matter is received.

Drawings

The drawings are objected to because the pictures of the gels in Fig. 3(A), Fig. 3(B), Fig. 4(A), and Fig. 4(B) are alleged to have poor resolution or perhaps too much protein. The Examiner indicated that these figures appear as solid black rectangles with the exception of a few white arrows which appear to point to areas of black within solid black rectangles.

Amended drawings were provided in the previously filed Office Action Response. However, since the Office Action Response was filed by facsimile transmission, it is possible that the quality of the drawings suffered, particularly if the drawings were then scanned at the Patent Office. The present response includes another set of replacement drawings. In the event that the quality of these drawings remains unacceptable to the Examiner, the Examiner is requested to examine the replacement drawings as actually filed in this response, rather than a scanned version thereof.

The Examiner is also requested to consider the fact that Fig. 3(A), 3(B), 4(A), and 4(B) represent black and white versions of photograph of stained 2D gels. It is in the nature of such gels to appear slightly dark, with areas of protein being even darker. However, Applicants submit that the drawings clearly show areas of protein that appear as irregularly shaped dark spots against a lighter gray background. Applicants would be willing to submit the drawings in color; however, this would simply replace the gray and black of the enclosed drawings with light blue and dark blue. Withdrawal of the rejection is respectfully requested.

Claim Objections

Claims 53-61 are objected to because the status of the claims is not identified. The present listing of the claims identifies these claims as being canceled.

Rejections under 35 U.S.C. § 102

Claims 32, 52, 62-69, 84, 89 and 104 of the above-referenced patent application stand rejected as being anticipated by Stausbøl-Grøn, et al., 391 *FEBS Letters* 71 (1996). This referenece is referred to as Brian, et al., in the Office Action and will be referred to as "Brian" herein.

The Office Action stated that Brian teaches a method comprising the step of removing at least two specific predefined proteins from a sample and recovering a modified sample and points to p. 72, col. 1 fifth paragraph, p. 73, col. 2, second paragraph, and the Abstract and specifically the recitation of the phrases "immunobead was washed", "Competitive proteins were...also added in solution", Fig. 2A, and "enrich selectively phage displayed antibodies directed against proteins constituting a difference between the two populations of cells" in support of this assertion. Applicants submit that Brian teaches placing an immunobead in an immunotube that contains a sample containing phage and soluble proteins, removing the immunobead from the immunotube, washing the immunobead, and eluting phage that had bound to the immunobead. The immunotube also has a mixture of proteins attached thereto (MIX). The immunobead has a mixture of proteins attached thereto (MIX + LDH). The sample also contains MIX proteins in solution. Applicants respectfully disagree that this paragraph teaches removal of two specific, predefined proteins from the sample for at least the following two reasons.

Firstly, there is no indication that any proteins bound to the immunobead during the incubation. Even if proteins did bind, washing the immunobead does not constitute removing two specific, predefined proteins from the sample because it is entirely unclear which proteins, if any, may have bound. During the phone interview, the Examiner alluded to the possibility that the antibodies displayed by the phage, which bound to the target proteins on the immunobead, could be considered to be "at least two specific, predefined proteins" such that removal of the phage bound to the beads constitutes removing at least two specific, predefined proteins from the sample. Applicants respectfully disagree. Even if the antibodies displayed by the phage could be considered to be "at least two specific, predefined proteins", Brian does not indicate that the phage that bound to the immunobeads did in fact display at least two different antibodies directed to the proteins

bound to the beads. Brian simply states that he was able to preferentially enrich for phage that bound to LDH and that after three rounds of selection, the results suggested non-significant binding against MIX proteins. (p. 73, right col., last paragraph). Thus the only evidence provided by Brian regarding antibodies displayed by the phage is that they bound to LDH. Brian does not say anything about antibodies that might bind to different proteins, and he does not characterize the antibodies that bound to LDH. Thus it is not seen how removal of the phage from the immunotube constitutes removal of at least two specific, predefined proteins as recited in the instant claims.

Secondly, as acknowledged by the Examiner, Brian does not teach recovery of a modified sample. Instead, Brian teaches recovery of phage that bound to the immunobeads. During the interview it was agreed that Applicants would specifically refer to this distinction between Brian and the claimed invention in the instant Office Action Response.

The Office Action mailed August 22, 2005, stated that Brian teaches that the removing step comprises "contacting the sample with an affinity binding composition ...comprising a first and second solid phase matrix contacting each other, wherein each solid phase comprises a plurality of particles." The Office Action indicated that the first solid phase matrix is the immunobeads and the second solid phase matrix is the immunotube. During the interview, the Examiner acknowledged that the immunotube is not a plurality of particles, and it was further pointed out that since the immunobeads all have the same mixture of proteins attached thereto, i.e., MIX+LDH or FM55p proteins, the immunobeads are not first and second solid phase matrices. For each of the above reasons, withdrawal of the rejection of these claims and claims dependent therefrom is respectfully requested.

Claims 32, 52, 62-69, 84-85, 88-89 and 104 stand rejected as being anticipated by U.S. Pat. No. 5,879,881, to Rubenstein, hereinafter "Rubenstein". The Office Action mailed August 22, 2005, stated that Rubenstein describes a method for separating proteins from a sample that contains proteins and recovering the modified sample comprising the steps of removing at least two specific predefined proteins and recovering a modified sample, wherein the removing step comprises contacting the sample with an affinity binding composition comprising a first and second solid phase matrix contacting each other, wherein each solid phase matrix comprises a plurality of particles, wherein the particles are present in a mixture, a first receptor immobilized on said first solid phase matrix, and a second receptor immobilized on said second solid phase matrix. The

Office Action referred specifically to col. 5, line 53 – col. 6, line 2, of Rubenstein. Applicants respectfully submit that Rubenstein does not teach the claimed invention for at least the following reasons.

Firstly, as discussed during the interview and acknowledged by the Examiner, col. 5, line 53 – col. 6, line 2 does not teach an affinity binding composition as recited in claim 63, comprising first and second solid phase matrices contacting each other, wherein each solid phase matrix comprises a plurality of particles, wherein the particles are present in a mixture, a first receptor immobilized on said first solid phase matrix *capable of specific binding to a first protein but not a second protein*, and a second receptor immobilized on said second solid phase matrix *capable of specific binding to the second protein but not the first protein* (emphasis added), or an affinity binding composition as recited in claim 84, comprising a plurality of solid phase matrices arranged such that each solid phase matrix is in contact with at least one other solid phase matrix; and a plurality of receptors having *different protein binding specificities*, wherein the receptors are immobilized on the plurality of solid phase matrices such that each solid phase matrix has a different protein binding specificity, wherein each solid phase matrix comprises a plurality of particles, and wherein the particles are present in the affinity binding composition as a mixture. As discussed during the interview and acknowledged by the Examiner, while Rubenstein does teach a mixture of microspheres having receptors attached thereto, Rubenstein not teach that the receptors on the microspheres in the mixture bind to *different proteins*. Rubenstein teaches that the receptors, e.g., monoclonal antibodies, may bind to different determinants or epitopes of *the antigen* (emphasis added). Thus if the antigen is a protein, the antibodies bind to the *same protein*, albeit to different portions thereof, in contrast to the instantly claimed invention. As discussed during the interview, Rubenstein's system is directed to the detection of a selected analyte in a fluid sample" (col. 2, lines 46-47). Therefore it would be disadvantageous to employ mixtures of microspheres having receptors capable of binding to different proteins attached thereto. Instead, Rubenstein teaches that if detection of at least two analytes is desired, "distinct groups of microspheres are entrapped within discrete zones of the porous matrix so as to permit performance of a multiple assay..." (col. 3, lines 10-15).

Secondly, Applicants continue to maintain that Rubenstein does not teach recovery of a modified sample within the meaning of the instant claims. As noted in the Office Action,

Rubenstein teaches that the fluid enters a second absorbent member following contact with the microspheres. It is clear from the instant specification and the fact that the claims recite recovering a modified sample *for analysis of remaining proteins* that the meaning of the phrase "recovering a modified sample" refers to recovery in a form that is suitable for further analysis of proteins remaining in the modified sample. There is no teaching in Rubenstein of removing the fluid from the second absorbent member so that it could be analyzed. There is also no teaching in Rubenstein that the second absorbent member should be changed or cleaned between uses of the device with different samples so that the user could meaningfully analyze proteins remaining in the fluid that enters the second absorbent member. Thus Applicants maintain that simply allowing the fluid to enter the second absorbent member in the device as described by Rubenstein, does not constitute "recovery of a modified sample" within the meaning of the instant claims.

In summary, Rubenstein does not teach recovery of a modified sample within the meaning of the instant claims and certainly does not teach use of an affinity binding composition having the features recited in the instant claims. Withdrawal of the rejection of claims 63 and 84 and claims dependent therefrom is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 32, 52, 62-69, 84-85, 88-89, and 104-107 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,137,808 to Ullman, hereinafter "Ullman", in view of Rubenstein. The Office Action stated that it would have been obvious to replace the affinity binding composition of Ullman with an affinity binding composition comprising particles. As discussed during the phone interview, Rubenstein does not teach an affinity binding composition as recited in the instant claims. Applicants respectfully submit that even had motivation to combine Rubenstein and Ullman existed, which it does not, replacing the affinity binding composition of Ullman with the affinity binding composition of Rubenstein would not render the claimed invention obvious.

In summary, there is no motivation to combine the teachings of Rubenstein and Ullman, and even if such a motivation existed, the resulting combination still would not teach each of the features of the claimed invention. Applicants therefore submit that the instant claims are not obvious for each of the foregoing reasons. Withdrawal of the rejection is respectfully requested.

In conclusion, in view of the remarks presented herein, none of the cited art anticipates any of the claims pending in the instant application nor renders them obvious. Applicants therefore respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5000 or (617) 248-5071 (direct dial).

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Respectfully submitted,

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Date: December 22, 2005

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